PATENT SPECIFICATION

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COMPLETE SPECIFICATION

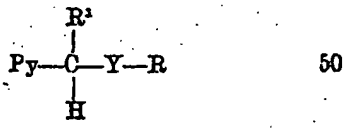
Antihistaminic Substances

We, SCHERING CORPORATION, a corporation of the State of New Jersey, of 2, Broad Street, Bloomfield, New Jersey, United States of America, (Assignees of NATHAN SPERBER, 1456, Minford Place, Bronx, New York, DOMENICK PAPA, 17th Avenue, Brooklyn, New York and ERWIN SCHWENK, 10, Crestmont Road, Montclair, New Jersey, United States of America), do hereby declare the nature of this invention and in what manner the same is to be performed to be particularly described and ascertained in and by the following statement:—

The invention relates to the manufacture of new substances of interesting and important physiological properties and more particularly to the manufacture of pyridyl substituted alkanes which have been found to be highly effective against histamine-induced allergic reactions.

It is recognized that the liberation of histamine into the tissues, which can be brought about by a multitude of agents or processes, is primarily responsible for many of the allergic manifestations in man. It has been found that certain substances of closely related chemical configurations are effective in alleviating the symptoms of many allergic reactions. The specificity of these chemical substances for the control of allergic reactions is well demonstrated by the researches carried on within the last ten years. However, although the substances prescribed at the present time represent a remarkable advance, they exhibit many undesirable side effects, or so-called toxic reactions, among which may be mentioned the high incidence of drowsiness, dizziness, nausea, gastro-intestinal irritation and dryness of the mouth.

It has been generally considered that only those substances which are derivatives of ethanolamine and ethylenediamine show pronounced anti-histaminic and antianaphylactic activity. It has now been found that pyridyl aliphatic amines of the general formula

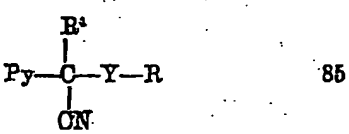


wherein Y stands for an alkylene group having 2 or 3 carbon atoms, Py is a pyridine ring which may be substituted by a halogen, alkoxy or lower alkyl group, R represents a dialkylamino, piperidino, morpholino, or iminazolinyl-group, and R^1 represents an alkyl, aryl, aralkyl *cyclo*alkyl or heterocyclic group or an alkyl, alkoxy, dialkylamino, chloro or bromo derivative of such groups, and the salts thereof with inorganic and organic acids, possess to an extremely high degree antihistaminic and antianaphylactic activity.

Throughout this Specification and claims it is to be understood that by the terms "alkyl," "alkoxy" (or "alkoxyl") and "dialkylamino" we mean groups in which the alkyl is a lower alkyl, i.e. contains not more than four carbon atoms.

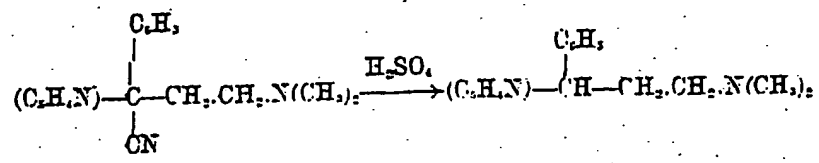
Clinical studies with representative members of the compounds of this invention have demonstrated extremely favorable antihistaminic activity. Particularly important is the comparative absence of any sedation, dizziness or depression in 85—90% of the cases treated. This advantage is of extreme importance in the clinical application of antihistaminic drugs.

The method of the invention comprises the hydrolysis and decarboxylation of the nitriles of the general formula



in which Py, Y, R and R' have the significance above mentioned.

When the nitriles are treated with a strong acid, the nitriles are hydrolysed and decarboxylated to the compounds of the invention as illustrated by the following equation:



Suitable nitriles for use in making the compounds of the invention may be made (as described in co-pending Application No. 25947/48 (Serial No. 666,778) by:

(a) condensing a pyridyl or alkylpyridyl halide with an alkane or substituted alkane nitrile to form a pyridyl alkane nitrile and thereafter condensing the latter product with a dialkylaminoalkyl halide, a piperidinoalkyl halide, a morpholinoalkyl halide, or an imidazolinylalkyl halide;

(b) condensing an alkane, or substituted alkane, nitrile with a dialkylaminoalkyl halide, a piperidinoalkyl halide, a morpholinoalkyl halide, or an imidazolinylalkyl halide and condensing the product with a pyridyl or alkylpyridyl halide; or

(c) condensing in one operation an alkane, or substituted alkane nitrile and a pyridyl or alkylpyridyl halide with a dialkylaminoalkyl halide, a piperidinoalkyl halide, a morpholinoalkyl halide, or an imidazolinylalkyl halide.

The condensations are advantageously effected by heating the reactants in an organic solvent, such as toluene or xylene or in liquid ammonia, in the presence of condensation catalysts, such as alkali metals, alkali metal amides, alkali metal alkoxides, or alkali metal organo compounds, for example, butyllithium or triphenylmethyl sodium.

The following specific example is illustrative of the method and products of the invention.

EXAMPLE.

3-PHENYL-3-(2'-PYRIDYL)-N,N-DIMETHYLPROPYLAMINE.

To 400 g. of α-phenyl-α-(β-dimethylaminoethyl)-2-pyridylacetonitrile there is added 2,000 g. of 80% sulfuric acid. The mixture is heated with stirring at 140—150° C. for 24 hours. After dilution with ice and water, the aqueous sulfuric acid solution is made alkaline with ammonia gas. The oil which separates out is extracted with ether, the extract is dried, and, after removing the ether, the residue is distilled giving the 3-phenyl-3-(2'-pyridyl)-N,N-dimethylpropylamine, b.p. 139—142° C./1—2 mm.

In addition to the hydrolysis and decarboxylation of the nitriles with 80% sulfuric acid, the conversion may be effected in other ways. For example:

(a) One part of the nitrile and ten parts of 48% hydrobromic acid are refluxed for a period of 50—60 hours. The aqueous hydrobromic acid is removed *in vacuo*. The residue is made alkaline with gaseous ammonia and the oil which separates is extracted with ether. The ether residue is treated with a saturated alcoholic solution of picric acid heated to boiling and filtered. The insoluble picrate is washed with boiling alcohol. This purification process removes any starting material which, unlike the amine, forms an alcohol soluble picrate. The insoluble picrate is then decomposed with dilute sodium hydroxide, the amine is isolated by extraction with ether and purified by distillation.

(b) To one part of the nitrile there is added five parts of 80% sulfuric acid and one part of 48% hydrobromic acid. The mixture is heated at a temperature of 130—140° C. for about 30—40 hours and the reaction mixture worked up as in method (a).

(c) One part of the nitrile is refluxed with concentrated hydrochloric acid for about 60 hours. The amine thus formed is isolated and purified as described under method (a).

The following compounds having substantial antihistaminic activity may be made from the corresponding nitriles by the methods of the Example:

3-Phenyl-3-(2'-pyridyl)-N,N-diethylpropylamine, a yellow oil boiling at 156° C./1 mm., from α-phenyl-α-(β-diethylaminoethyl)-2-pyridylacetonitrile.

4-Phenyl-3-(2'-pyridyl)-N,N-dimethylbutylamine, boiling at about 135° C./0.5 mm., from α-benzyl-α-(β-dimethylaminoethyl)-2-pyridylacetonitrile.

3-(2'-Thienyl)-3-(2'-pyridyl)-N,N-dimethylpropylamine, a pale yellow oil boiling at 154° C./2 mm., from α-(2'-thienyl)-α-(β'-dimethylaminoethyl)-2-pyridylacetonitrile.

4-(2¹¹-Thienyl)-3-(2¹-pyridyl)-N,N-dimethylbutylamine, boiling at 130—133° C./0.1 mm., from α-(2¹-thienylmethyl)-α-(β¹-dimethylaminoethyl)-2-pyridylacetonitrile.

3-(*p*-Methylphenyl)-3-(2¹-pyridyl)-N,N-dimethylpropylamine, boiling at about 130—135° C./0.5 mm., from α-(*p*-methylphenyl)-α-(β¹-dimethylaminoethyl)-2-pyridylacetonitrile.

3-(*p*-Methoxyphenyl)-3-(2¹-pyridyl)-N,N-dimethylpropylamine, boiling at about 137—142° C./0.5 mm., from α-(*p*-Methoxyphenyl)-α-(β¹-dimethylaminoethyl)-2-pyridylacetonitrile.

3-(*p*-Isopropylphenyl)-3-(2¹-pyridyl)-N,N-dimethylpropylamine, boiling at 144—147° C./1mm., from α-(*p*-isopropylphenyl)-α-(β¹-dimethylaminoethyl)-2-pyridylacetonitrile.

3-Phenyl-3-(6¹-methyl-2¹-pyridyl)-N,N-dimethyl-propylamine, boiling at 171—175° C./1 mm., from α-(β¹-dimethylaminoethyl)-α-(6-methyl-2-pyridyl)-phenylacetonitrile.

3-(*p*-Bromophenyl)-3-(2¹-pyridyl)-N,N-dimethylpropylamine, boiling at about 147—152° C./0.5 mm., from α-(*p*-bromophenyl)-α-(β¹-dimethylaminoethyl)-2-pyridylacetonitrile.

4-Phenyl-4-(2¹-pyridyl)-2-(dimethylamino)-butane, from α-phenyl-α-(2-pyridyl)-γ-(dimethylamino)-valeronitrile.

4-Phenyl-4-(2¹-pyridyl)-N,N-dimethylbutylamine, from α-phenyl-α-(2-pyridyl)-γ-(dimethylaminomethyl)-butyronitrile.

3-Phenyl-2-(2¹-pyridyl)-N,N-dimethylpropylamine, from α-benzyl-α-(2-pyridyl)-β-dimethylaminopropionitrile.

3-Cyclohexyl-3-(2¹-pyridyl)-N,N-dimethylpropylamine, from α-cyclohexyl-α-(β¹-dimethylaminoethyl)-2-pyridylacetonitrile.

3-Cyclohexyl-4-(2¹-pyridyl)-N,N-dimethylbutylamine, from β-cyclohexyl-α-(β-dimethylaminoethyl)-α-(2-pyridyl)-propionitrile.

3-(5¹¹-Bromo-2¹¹-thienyl)-3-(2¹-pyridyl)-N,N-dimethylpropylamine, from α-(5-bromo-2-thienyl)-α-(β¹-dimethylaminoethyl)-2-pyridylacetonitrile.

4-(*p*-Bromophenyl)-3-(2¹-pyridyl)-N,N-dimethylbutylamine, from α-(*p*-bromobenzyl)-α-(β¹-dimethylaminoethyl)-2-pyridylacetonitrile.

The compounds of the invention may be used in the form of the free bases or in the form of the salts thereof with inorganic acids such as hydrochloric, hydrobromic, sulfuric and phosphoric acids, and organic acids, such as salicylic, tartaric, maleic, succinic, citric and lactic acids.

Typical examples of salts of the 3-phenyl-3-(2¹-pyridyl)-N,N-dimethylpropylamine of the Example are the following:

1. The mono-hydrochloride is obtained by passing anhydrous hydrochloric acid into an ether solution of the γ-phenyl-γ-(2-pyridyl)-N,N-dimethylpropylamine. The hydrochloride can be recrystallized from absolute alcohol and absolute ether and melts at 117—119° C.

2. The tartrate of the compound of Example I is obtained in the usual manner and melts at 114—115° C.

3. The mono-hydrogen oxalate is prepared in ethanol and after recrystallization from acetone melts at 152—152.5° C.

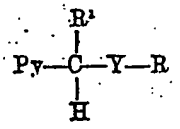
4. The mono-hydrogen succinate is prepared in a manner similar to the mono-hydrogen oxalate in ethyl alcohol solution and after recrystallization from pentanol melts at 99.5—100° C.

5. The mono-hydrogen maleate is similarly prepared and after recrystallization from pentanol, melts at 106—107° C.

The compounds may be used in a variety of forms, such as tablets for oral administration, creams for topical application, and injectible solutions. Preferably the salts of the compounds are used in the creams which may be of the usual formulations. The injectible solutions preferably comprise non-toxic salts in admixture with sodium carbonate and boric acid and are sterilized before use.

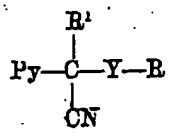
Having now particularly described and ascertained the nature of our said invention and in what manner the same is to be performed, we declare that what we claim is:—

1. A process for the manufacture of antihistaminic substances of the general formula:



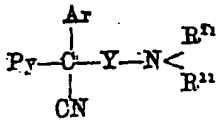
where Py represents a pyridine residue which may carry halogen, alkyl or alkoxy as substituents, Y stands for an alkylene group having 2 or 3 carbon atoms, R represents a dialkylamino-, piperidino-, morpholino- or iminazolino-group and R¹ stands for alkyl, aryl, aralkyl, cycloalkyl or a heterocyclic residue, which may carry as substituents alkyl, alkoxyl, dialkylamino, chlorine or bromine, and of salts of such compounds, said process comprising the hydrolysis and decarboxylation of a nitrile having

the formula:—



by reaction with a strong acid, e.g. with 80% sulphuric acid.

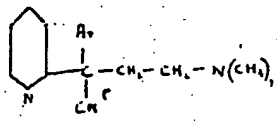
2. A process as claimed in Claim 1 in which the nitrile has the formula



where Py and Y have the same significance as in Claim 1, Ar stands for an aryl group, and either R^{11} is an alkyl group or $N<^{R^{11}}_{R^{11}}$ stands for a piperidine residue.

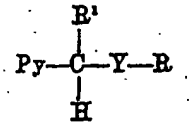
3. A process as claimed in Claim 2 in which Py is 2-pyridyl, Ar is phenyl or *p*-chlorophenyl, and R^{11} is methyl.

4. A process for the manufacture of 3-phenyl- and 3-*p*-chlorophenyl - 3 - (2'-pyridyl) - N,N - dimethylpropylamines, and of salts of these, by hydrolysis and decarboxylation of the nitriles of formula



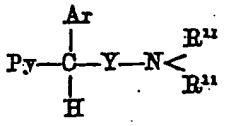
(where Ar stands for phenyl or *p*-chlorophenyl) by reaction with a strong acid, e.g. with 80% sulphuric acid, the base produced being converted into salts as desired.

5. Compounds of the formula:



where Py, R and R^1 have the same significance as in Claim 1 and salts thereof whenever produced by the process of any of the preceding claims or by an obvious chemical equivalent of such process.

6. Compounds of the formula:



in which Py and Y have the same significance as in Claim 1, Ar stands for phenyl, a chlorophenyl, an alkylphenyl or an alkoxyphenyl, and R^{11} stands for alkyl and salts thereof whenever produced by the process of any of Claims 1—4 or by an obvious chemical equivalent of such process.

7. Compounds as claimed in Claim 6 in which Ar is phenyl or *p*-chlorophenyl, Y is $.CH_2.CH_2.$ and R^{11} is methyl, and salts thereof, whenever produced by the process of any of Claims 1—4 or by an obvious chemical equivalent of such process.

8. Compounds as claimed in Claim 6 in which Py is 2-pyridyl, Y is $.CH_2.CH_2.$, and $N<^{R^{11}}_{R^{11}}$ stands for a dialkylamino group or for the N-piperidino radical, and salts thereof, whenever produced by the process of any of Claims 1—4 or by an obvious chemical equivalent of such process.

Dated this 18th day of October, 1948.

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